Cardiac spectroscopy in chronic fatigue syndrome (CFS) correlates with autonomic abnormalities on standing and stratifies oxidative function in skeletal muscle

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Introduction Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a major clinical problem affecting a substantial number of predominantly young individuals through its impact on quality of life and social function. To date, little progress has been made in terms of identifying aetiological processes in CFS/ME. This failure to elucidate key mechanisms has impaired the development of successful therapeutic approaches for this important condition. The strongest body of evidence for organic dysfunction in CFS/ME relates to impairment of autonomic nervous system function and cardiac output [1,2]. Despite this, high-energy phosphate cardiac energetics have never been assessed or related to the measured autonomic nervous system abnormalities. In addition, previous studies of muscle exercise metabolism in CFS subjects by ^{31}P MRS have been inconclusive and have suggested that the subjects studied are not homogenous in metabolic response [3,4,5,6]. This study, for the first time, relates cardiac energetics by ^{31}P MRS to measures of autonomic response and then uses sub-grouping according to cardiac energetics to examine muscle energetics.

Methods *Recruitment:* 12 female CFS/ME patients (diagnosed in the last 2 years according to the Fukuda criteria [7]) and 8 age-matched female controls were recruited under local ethics approval. *MR protocol:* Cardiac high-energy phosphate metabolism was measured using ^{31}P MRS using a 3T Intera Achieva scanner (Philips, Best, NL) with a 10cm diameter ^{31}P surface coil (Pulseteq, UK). Subjects were placed in a prone position and after confirming the location of the heart, shimming was performed using a cardiac triggered, breath-held field map [8]. A slice-selective, cardiac gated 1-dimensional chemical shift imaging (1D-CSI) sequence was used with a 7cm slice selective pulse applied foot head to eliminate contamination from the liver, with spatial pre-saturation of lateral skeletal muscle to avoid spectral contamination. 16 coronal phase-encoding steps were used, each 10mm thick (TR = heart rate, 192 averages with acquisition weighting approx. 20 mins acquisition time). The first spectrum arising entirely beyond the chest wall was selected. Quantification of phosphocreatine (PCr), the γ resonance of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) was performed using the AMARES time domain fit routine. After fitting the ATP peak area was corrected for blood contamination by 1/6 of the amplitude of the combined 2,3-DPG peak [9], and the PCr/ATP ratios were calculated and corrected for saturation, with T_1 values taken from the literature [10]. Flip angle correction was made using a gadolinium-doped 20mM phenyl phosphonic acid phantom at the centre of the coil [11,12]. *Muscle MRS :* Muscle MRS data were acquired with a 14cm diameter ^{31}P surface coil. A purpose-built apparatus permitted a controlled plantar flexion between 0º (foot vertical) and 30º to exercise the soleus and gastrocnemius muscles. Subjects performed an exercise protocol, consisting of three minutes rest, three minutes of plantar flexion at 0.5 Hz and 3 minutes of rest to measure recovery to equilibrium. Two exercises were performed with fixed loads of 25% and 35% of the Maximum Voluntary Contraction (determined prior to spectroscopy) to produce anaerobic metabolism and allow evaluation of pH handling. Phosphorus spectra were collected at 10s intervals throughout the exercises using an adiabatic 1D-ISIS sequence to localise signal. The AMARES time domain fit was used. A single exponential fit was used to estimate the half time for PCr and ADP recovery.

Autonomic nervous function : Haemodynamic responses to standing were recorded in response to a head-up tilt protocol which raised the patient from supine to a 70º stand in order to apply an orthostatic challenge. All cardiovascular assessments were carried out with continuous heart rate and beat to beat blood pressure measurement (Taskforce:CNSystems). In particular, the change in cardiac index (cardiac output standardized for body surface area) and the total peripheral resistance (which is an indicator of afterload i.e. the pressure against which the heart must pump) were measured.

Results The mean cardiac PCr/ATP ratio in CFS/ME tended to be lower than the control group but fails to reach statistical significance (p = 0.07, fig 1a). The CFS/ME group contained individuals with normal and sub-normal cardiac energetics. The CFS/ME group was divided in two based on the median PCr/ATP ratio, forming a low PCr/ATP ratio group (1.57 ± 0.22) and a group with normal PCr/ATP ratio (1.90 ± 0.09) when compared with age-matched controls (PCr/ATP ratio 1.90 ± 0.10, fig 1b). The oxidative and acid handling parameters from the muscle MRS were then analysed in these groups. Those CFS/ME subjects with impaired cardiac energetics also have impaired oxidative function compared with controls, as measured by lengthened half-time for both PCr and ADP recovery (figs 1c and 1d). The PCr/ATP ratio was strongly correlated with both half times (with PCr: $\kappa = -0.71$, p = 0.005, and ADP $\kappa = -0.60$, p = 0.02). In comparison with those autonomic parameters which change on the orthostatic stress imposed by standing, impaired PCr/ATP on standing correlates with impairment in the cardiac index change on standing (fig 1e) and with increased change in total peripheral resistance on standing (fig 1f).

Conclusions CFS/ME patients have heterogeneous results on muscle ^{31}P MRS ranging normal to sub-normal, but grouping those results by cardiac energetics can identify sub-groups with normal and sub-normal oxidative metabolism. Impaired cardiac metabolism at rest was found to be indicative of impaired performance on standing.

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(a) Cardiac PCr/ATP ratio (-); CFS vs Control. (b) Cardiac PCr/ATP ratio (-); CFS low PCr/ATP, CFS high PCr/ATP, Control; p = 0.008, p = 0.004. (c) Half-time of PCr recovery (s); CFS low PCr/ATP, CFS high PCr/ATP, Control; p = 0.04. (d) Half-time of ADP recovery (s); CFS low PCr/ATP, CFS high PCr/ATP, Control; p = 0.02. (e) Change in cardiac index on standing vs PCr/ATP; p=0.03. (f) Change in TPR on standing vs PCr/ATP; p=0.02.